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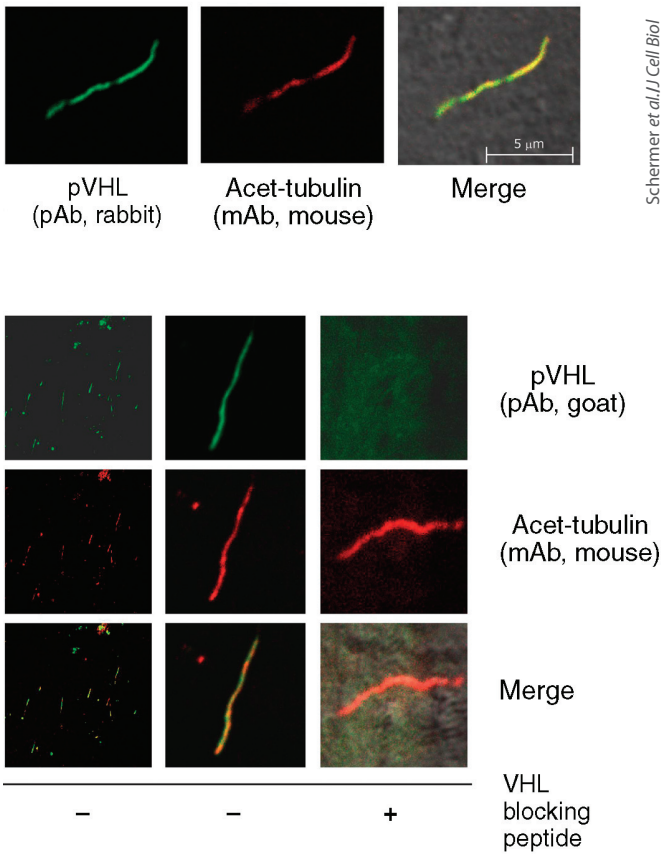
The von Hippel-Lindau protein controls ciliogenesis

The tumor syndrome von Hippel-Lindau (VHL) disease is caused by heterozygous germline inactivation of the *VHL* tumor suppressor gene. The cardinal feature of this hereditary cancer syndrome is development of multiple vascular tumors (hemangioblastomas) in the central nervous system and retina combined with clear-cell carcinoma of the kidney and pheochromocytoma. VHL disease is an autosomal-dominant disorder, and tumor development in VHL disease is linked to somatic inactivation of the remaining wild-type *VHL* allele, leading to loss of the wild-type *VHL* gene product, VHL protein (pVHL). In the kidney, this event not only precipitates the development of clear-cell carcinoma but is also associated with the growth of premalignant renal cysts; the pathogenesis of cystic kidney disease in VHL disease patients is unknown. Over the last few years, the pathogenesis of other cystic kidney diseases has been linked to the monocilia of kidney cells. Cilia are highly conserved organelles that project from the surfaces of many cells. The essential structure of renal monocilia consists of nine peripheral microtubule doublets forming the axoneme and surrounded by a membrane lipid bilayer that is continuous with the plasma membrane. Cilia are sensory organelles and have been shown to be involved in mechanosensation, photoperception, and osmosignaling. The assembly and maintenance of cilia are mediated by intraflagellar transport, a bidirectional microtubule-based transport system.



Schermer *et al.J Cell Biol*

pVHL is localized to cilia of Madin-Darby canine kidney cells. pAb, polyclonal antibody; mAb, monoclonal antibody.

In a recent study, Schermer *et al.* demonstrated that pVHL localizes to the monocilia of kidney cells and controls ciliogenesis. Knock-down of pVHL impeded the formation of cilia in mouse inner medullary collecting duct kidney cells, whereas the expression of pVHL in VHL-negative renal cancer cells rescued the ciliogenesis defect. Using green fluorescent protein-tagged end-binding protein 1 to label microtubule plus ends, these authors found that pVHL does not affect the microtubule growth rate but is needed to orient the growth of microtubules toward the cell periphery, a prerequisite for the formation of cilia.

A role of pVHL in regulating ciliogenesis has previously been documented and, together with these results, could explain why VHL disease patients can develop polycystic kidney disease. Although much is known about the role of pVHL in tumorigenesis at the molecular level, the pathogenesis of premalignant kidney cysts in VHL disease patients has remained elusive, and the finding that pVHL plays a critical role in ciliogenesis sheds new light on the pathogenesis of premalignant kidney cysts in VHL disease patients. (*J Cell Biol* 2006; **175**: 547–554)

Juan Oliver

Angiotensin II causes hypertension and cardiac hypertrophy through its receptors in the kidney

Despite decades of scrutiny, the precise pathogenesis of essential hypertension has been difficult to delineate. Guyton and his associates suggested that defective handling of sodium by the kidney and consequent dysregulation of body fluid volumes is a requisite, final common pathway in hypertension pathogenesis. The powerful capacity of this pathway to modulate blood pressure is illustrated by the elegant studies of Lifton and associates showing that virtually all of the mendelian disorders with major impact on blood pressure homeostasis are caused by genetic variants affecting salt and water reabsorption by the distal nephron. However, other studies have suggested that primary vascular defects may cause hypertension by impacting peripheral resistance without direct involvement of renal excretory functions.

Among the various regulatory systems that impact blood pressure, the renin–angiotensin system has a key role. Inappropriate activation of the system, as in renal artery stenosis, leads to profound hypertension and cardiovascular

morbidity. Moreover, in patients with essential hypertension, who typically lack overt signs of renin activation, inhibitors of the system effectively reduce blood pressure, suggesting that dysregulation of the renin–angiotensin system contributes to their elevated blood pressure.

The effects of angiotensin II to increase blood pressure are mediated by type I (AT_1) angiotensin receptors, and these receptors are expressed in a variety of organ systems thought to play key roles in blood pressure homeostasis, including the heart, kidney, blood vessels, adrenal glands, and cardiovascular control centers in the brain. For example, stimulation of AT_1 receptors in the vasculature causes potent vasoconstriction and, in the adrenal cortex, causes release of aldosterone that in turn promotes sodium reabsorption in the distal nephron. In the brain, intraventricular injection of angiotensin II causes a dramatic pressor response that is also mediated by AT_{1A} receptors. In the kidney, activation of AT_1 receptors is associated with renal vasoconstriction and antinatriuresis. Nevertheless, whether angiotensin actions in these individual tissue sites contribute *in vivo* to the pathogenesis of hypertension and its complications is not clear.

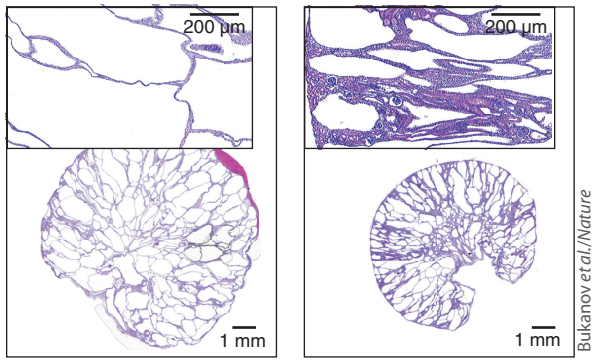
To address this question, Crowley *et al.* used a kidney cross-transplantation strategy to separate the actions of AT_1 receptor pools in the kidney from those in systemic tissues. Kidney transplantation was carried out between genetically matched wild-type mice and mice homozygous for a targeted disruption of the *Agtr1a* gene locus encoding the AT_{1A} receptor. The AT_{1A} receptor is the major AT_1 receptor isoform in the mouse and the closest mouse homologue to the human AT_1 receptor gene. The authors found that renal AT_1 receptors are required for the development of angiotensin II-dependent hypertension and cardiac hypertrophy. That is, when AT_1 receptors are eliminated from the kidney, the residual repertoire of systemic, extrarenal AT_1 receptors is not sufficient to induce hypertension or cardiac hypertrophy. These findings demonstrate the critical role of the kidney in the pathogenesis of hypertension and its cardiovascular complications. They also show that cardiac hypertrophy depends on blood pressure elevation rather than expression of AT_1 receptors in the heart. Finally, they suggest that the major mechanism of action of inhibitors of angiotensin in hypertension is attenuation of angiotensin II effects in the kidney. (*Proc Natl Acad Sci USA* 2006; **103**: 17985–17990)

Detlef Schlöndorff

Long-lasting arrest of murine polycystic kidney disease with a cyclin-dependent kinase inhibitor

Polycystic kidney diseases (PKDs) are primarily characterized by the growth of fluid-filled cysts in renal tubules, leading to end-stage renal disease. Mutations in the *PKD1* or *PKD2* gene lead to autosomal-dominant PKD (ADPKD), a slowly developing adult form. Autosomal-recessive PKD results from mutations in the *PKHD1* gene, affecting newborn infants and progressing very rapidly. No effective treatment is currently available for these diseases. All proteins known to be disrupted in PKD were recently localized to the primary cilia. Because ciliary functions seem to include cell-cycle regulation, disruption of proteins associated with cilia may directly affect the cell cycle and proliferation, resulting in cystic disease.

Bukanov *et al.* reasoned that the dysregulated cell cycle may be the most proximal cause of cystogenesis, and that intervention targeted at this point could provide significant therapeutic benefit for PKD. In a recent article, the authors



(*R*)-Roscovitine effectively attenuates disease progression in *cpk* mice.

examined the effect of treatment with (*R*)-roscovitine, a potent cyclin-dependent kinase (CDK) inhibitor, on the slowly progressive renal cystic disease in *jck* mice. Development of PKD in the *jck* mice resembles that of human disease in many ways, with cysts developing in multiple nephron segments and with more aggressive disease in males. (*R*)-Roscovitine, currently in clinical trials as an anticancer agent, inhibits Cdk2–cyclin E as well as Cdk7–cyclin H, Cdk9–cyclin T1, and Cdk5–p35–p25.

The authors found that treatment with (*R*)-roscovitine effectively arrested cystic disease in *jck* as well as *cpk* mouse models of PKD. Continuous daily administration of the drug was not required to achieve efficacy; pulse treatment provided a robust, long-lasting effect, indicating potential clinical benefits for a lifelong therapy. Molecular studies of the mechanism of action revealed effective cell-cycle arrest, transcriptional inhibition, and attenuation of apoptosis. The authors also found that (*R*)-roscovitine was active against cysts originating from different parts of the nephron, a desirable feature for the treatment of ADPKD, in which cysts form in multiple nephron segments. These results indicate that inhibition of CDK is a new and effective approach to the treatment of PKD in mice, and they highlight the therapeutic potential for cell-cycle inhibition for the treatment of PKD in humans. (*Nature* 2006; **444**: 949–952)

Juan Oliver